CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074550

Trade Name : GLIPIZIDE TABLETS USP

Generic Name: Glipizide Tablets USP 5mg and 10mg

Sponsor : Duramed Pharmaceuticals ,Inc.

Approval Date: September 11, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074550

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074550

APPROVAL LETTER

ANDA 74-550

9/11/97

Duramed Pharmaceuticals, Inc.
Attention: John R. Rapoza
5040 Lester Road
Cincinnati, Ohio 45213

Dear Sir:

This is in reference to your abbreviated new drug application dated October 10, 1994, submitted pursuant to Section 505(j) of the Food, Drug, and Cosmetic Act, for Glipizide Tablets USP, 5 mg and 10 mg.

Reference is also made to your amendments dated August 5, and September 2, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Glipizide Tablets USP, 5 mg and 10 mg to be bioequivalent and, therefore, therapeutically equivalent to those of the listed drug (Glucotrol® Tablets, 5 mg and 10 mg, respectively, of Pfizer Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of these drugs.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

9-12-97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074550

FINAL PRINTED LABELING

Each tablet contains:
Glipizide, USP ..... 5 mg
USUAL DOSAGE: See insert.
Do not store above 30°C (86°F).
Dispense in a tight container as defined in the USP.

Lot No.:

Exp. Date:

DURAmed

NDC 51285-598-02

Glipizide

Tablets, USP

5 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 Tablets

DURAMED PHARMACEUTICALS, INC.
CINCINNATI, OH 45213 USA
L00542 ISS. 5/97

0 28176 59802 2

Each Tablet Contains:
Glipizide, USP ..... 5 mg
USUAL DOSAGE: See insert.
Do not store above 30°C (86°F).
Dispense in a tight container as defined in the USP.

Lot No.:

Exp. Date:

DURAmed

NDC 51285-598-04

Glipizide

Tablets, USP

5 mg

CAUTION: Federal law prohibits dispensing without prescription.

500 Tablets

DURAMED PHARMACEUTICALS, INC.
CINCINNATI, OH 45213 USA
L00543 ISS. 5/97

0 28176 59804 6

Each Tablet Contains:
Glipizide, USP ..... 5 mg
USUAL DOSAGE: See insert.
Do not store above 30°C (86°F).
Dispense in a tight container as defined in the USP.

Lot No.:

Exp. Date:

DURAmed

NDC 51285-598-05

Glipizide

Tablets, USP

5 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 Tablets

DURAMED PHARMACEUTICALS, INC.
CINCINNATI, OH 45213 USA
L00544 ISS. 5/97

0 28176 59805 3

Each Tablet Contains:
Glipizide, USP ..... 10 mg
USUAL DOSAGE: See insert.
Do not store above 30°C (86°F).
Dispense in a tight container as defined in the USP.

Lot No.:

Exp. Date:

DURAmed

NDC 51285-599-02

Glipizide

Tablets, USP

10 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 Tablets

DURAMED PHARMACEUTICALS, INC.
CINCINNATI, OH 45213 USA
L00545 ISS. 5/97

0 28176 59902 9

Lot No.:

Exp. Date:

Each Tablet Contains:
Glipizide, USP ..... 10 mg

USUAL DOSAGE: See insert.
Do not store above 30°C (86°F).
Dispense in a tight container as defined in the USP.

DURAmed

NDC 51285-599-04

Glipizide

Tablets, USP

10 mg

CAUTION: Federal law prohibits dispensing without prescription.

500 Tablets

DURAMED PHARMACEUTICALS, INC.
CINCINNATI, OH 45213 USA
L00546 ISS. 5/97

0 28176 59904 3

Lot No.:

Exp. Date:

Each Tablet Contains:
Glipizide, USP ..... 10 mg

USUAL DOSAGE: See insert.
Do not store above 30°C (86°F).
Dispense in a tight container as defined in the USP.

DURAmed

NDC 51285-599-05

Glipizide

Tablets, USP

10 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 Tablets

DURAMED PHARMACEUTICALS, INC.
CINCINNATI, OH 45213 USA
L00547 ISS. 5/97

0 28176 59905 0

DURAMED PHARMACEUTICALS, INC.

CAUTION: Federal law prohibits dispensing without a prescription.

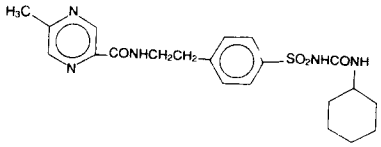
GLIPIZIDE TABLETS, USP

For Oral Use

DESCRIPTION

Glipizide is an oral blood-glucose-lowering drug of the sulfonylurea class.

The Chemical Abstracts name of glipizide is 1-Cyclohexyl-3-[[*p*-[2-(5-methylpyrazinecarboxamido)ethyl]phenyl]sulfonyl]urea. The molecular formula is $C_{21}H_{27}N_5O_4S$; the molecular weight is 445.55; the structural formula is shown below:



Glipizide is a whitish, odorless powder with a pKa of 5.9. It is insoluble in water and alcohols, but soluble in 0.1 *N* NaOH; it is freely soluble in dimethylformamide.

Each tablet, for oral administration, contains 5 mg or 10 mg glipizide. In addition, each tablet contains the following inactive ingredients: anhydrous lactose, microcrystalline cellulose, corn starch, silicon dioxide, stearic acid.

CLINICAL PHARMACOLOGY

Mechanism of Action: The primary mode of action of glipizide in experimental animals appears to be the stimulation of insulin secretion from the beta cells of pancreatic islet tissue and is thus dependent on functioning beta cells in the pancreatic islets. In humans glipizide appears to lower the blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. The mechanism by which glipizide lowers blood glucose during long-term administration has not been clearly established. In man, stimulation of insulin secretion by glipizide in response to a meal is undoubtedly of major importance. Fasting insulin levels are not elevated even on long-term glipizide administration, but the postprandial insulin response continues to be enhanced after at least 6 months of treatment. The insulinotropic response to a meal occurs within 30 minutes after an oral dose of glipizide in diabetic patients, but elevated insulin levels do not persist beyond the time of the meal challenge. Extrapancreatic effects may play a part in the mechanism of action of oral sulfonylurea hypoglycemic drugs.

Blood sugar control persists in some patients for up to 24 hours after a single dose of glipizide, even though plasma levels have declined to a small fraction of peak levels by that time (see Pharmacokinetics below).

Some patients fail to respond initially, or gradually lose their responsiveness to sulfonylurea drugs, including glipizide. Alternatively, glipizide may be effective in some patients who have not responded or have ceased to respond to other sulfonylureas.

Other Effects:

It has been shown that glipizide therapy was effective in controlling blood sugar without deleterious changes in the plasma lipoprotein profiles of patients treated for NIDDM.

In a placebo-controlled, crossover study in normal volunteers, glipizide had no anti-diuretic activity, and, in fact, led to a slight increase in free water clearance.

Pharmacokinetics:

Gastrointestinal absorption of glipizide in man is uniform, rapid, and essentially complete. Peak plasma concentrations occur 1-3 hours after a single oral dose. The half-life of elimination ranges from 2-4 hours in normal subjects, whether given intravenously or orally. The metabolic and excretory patterns are similar with the two routes of administration, indicating that first-pass metabolism is not significant. Glipizide does not accumulate in plasma on repeated oral administration. It has been reported that total absorption and disposition of an oral dose was unaffected by food in normal volunteers, but absorption was delayed by about 40 minutes. Thus glipizide was more effective when administered about 30 minutes before, rather than with, a test meal in diabetic patients. Protein binding was studied in serum from volunteers who received either oral or intravenous glipizide and found to be 98-99% one hour after either route of administration. The apparent volume of distribution of glipizide after intravenous administration was 11 liters, indicative of localization within the extracellular fluid compartment. In mice no glipizide or metabolites were detectable autoradiographically in the brain or spinal cord of males or females, nor in the fetuses of pregnant females. In another study, however, very small amounts of radioactivity were detected in the fetuses of rats given labelled drug.

The metabolism of glipizide is extensive and occurs mainly in the liver. The primary metabolites are inactive hydroxylation products and polar conjugates and are excreted mainly in the urine. Less than 10% unchanged glipizide is found in the urine.

INDICATIONS AND USAGE

Glipizide Tablets, USP are indicated as an adjunct to diet for the control of hyperglycemia and its associated symptomatology in patients with non-insulin-dependent diabetes mellitus (NIDDM; type II), formerly known as maturity-onset diabetes, after an adequate trial of dietary therapy has proved unsatisfactory.

In initiating treatment for non-insulin-dependent diabetes, diet should be emphasized as the primary form of treatment. Caloric restriction and weight loss are essential in the obese diabetic patient. Proper dietary management alone may be effective in controlling the blood glucose and symptoms of hyperglycemia. The importance of regular physical activity should also be stressed, and cardiovascular risk factors should be identified, and corrective measures taken where possible.

If this treatment program fails to reduce symptoms and/or blood glucose, the use of an oral sulfonylurea or insulin should be considered.

Use of glipizide must be viewed by both the physician and patient as a treatment in addition to diet, and not as a substitute for diet or as a convenient mechanism for avoiding dietary restraint. Furthermore, loss of blood glucose control on diet alone also may be transient, thus requiring only short-term administration of glipizide.

During maintenance programs, glipizide should be discontinued if satisfactory lowering of blood glucose is no longer achieved. Judgments should be based on regular clinical and laboratory evaluations.

In considering the use of glipizide in asymptomatic patients, it should be recognized that controlling the blood glucose in non-insulin-dependent diabetes has not been definitely established to be effective in preventing the long-term cardiovascular or neural complications of diabetes.

CONTRAINDICATIONS

Glipizide Tablets, USP are contraindicated in patients with:

1. Known hypersensitivity to the drug.
2. Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.

WARNINGS

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY:

The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups (*Diabetes*, 19, supp. 2: 747-830, 1970).

UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2 1/2 times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of glipizide and of alternative modes of therapy.

Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

PRECAUTIONS

General

Renal and Hepatic Disease: The metabolism and excretion of glipizide may be slowed in patients with impaired renal and/or hepatic function. If hypoglycemia should occur in such patients, it may be prolonged and appropriate management should be instituted.

Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Proper patient selection, dosage, and instructions are important to avoid hypoglycemic episodes. Renal or hepatic insufficiency may cause elevated blood levels of glipizide and the latter may also diminish gluconeogenic capacity, both of which increase the risk of serious hypoglycemic reactions. Elderly, debilitated or malnourished patients, and those with adrenal or pituitary insufficiency are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used.

Loss of Control of Blood Glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur. At such times, it may be necessary to discontinue glipizide and administer insulin.

The effectiveness of any oral hypoglycemic drug, including glipizide, in lowering blood glucose to a desired level decreases in many patients over a period of time, which may be due to progression of the severity of the diabetes or to diminished responsiveness to the drug. This phenomenon is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective in an individual patient when first given.

Laboratory Tests:

Blood and urine glucose should be monitored periodically. Measurement of glycosylated hemoglobin may be useful.

Information for Patients:

Patients should be informed of the potential risks and advantages of glipizide and of alternative modes of therapy. They should also be informed about the importance of adhering to dietary instructions, of a regular exercise program, and of regular testing of urine and/or blood glucose.

The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members. Primary and secondary failure should also be explained.

Drug Interactions:

The hypoglycemic action of sulfonylureas may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents, some azoles and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, and beta-adrenergic blocking agents. When such drugs are administered to a patient receiving glipizide, the patient should be observed closely for hypoglycemia. When such drugs are withdrawn from a patient receiving glipizide, the patient should be observed closely for loss of control. *In vitro* binding studies with human serum proteins indicate that glipizide binds differently than tolbutamide and does not interact with salicylate or dicumarol. However, caution must be exercised in extrapolating these findings to the clinical situation and in the use of glipizide with these drugs.

Certain drugs tend to produce hyperglycemia and may lead to loss of control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving glipizide, the patient should be closely observed for loss of control.

When such drugs are withdrawn from a patient receiving glipizide, the patient should be observed closely for

A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the intravenous, topical, or vaginal preparations of miconazole is not known. The effect of concomitant administration of fluconazole and glipizide was reported in a placebo-controlled crossover study in normal volunteers. All subjects received glipizide alone and following treatment with 100 mg of fluconazole as a single daily oral dose for 7 days. The mean percentage increase in the glipizide AUC after fluconazole administration was 56.9% (range: 35 to 81).

Carcinogenesis, Mutagenesis, Impairment of Fertility:
A twenty month study in rats and an eighteen month study in mice at doses up to 75 times the maximum human dose revealed no evidence of drug-related carcinogenicity. Bacterial and *in vivo* mutagenicity tests were uniformly negative. Studies in rats of both sexes at doses up to 75 times the human dose showed no effects on fertility.

Pregnancy: Teratogenic Effects:
Pregnancy Category C:
Glipizide was found to be mildly fetotoxic in rat reproductive studies at all dose levels (5-50 mg/kg). This fetotoxicity has been similarly noted with other sulfonylureas, such as tolbutamide and tolazamide. The effect is perinatal and believed to be directly related to the pharmacologic (hypoglycemic) action of glipizide. In studies in rats and rabbits no teratogenic effects were found. There are no adequate and well controlled studies in pregnant women. Glipizide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Because recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, many experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nonteratogenic Effects: Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives. If glipizide is used during pregnancy, it should be discontinued at least one month before the expected delivery date.

Nursing Mothers:
Although it is not known whether glipizide is excreted in human milk, some sulfonylurea drugs are known to be excreted in human milk. Because the potential for hypoglycemia in nursing infants may exist, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. If the drug is discontinued and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

Pediatric Use:
Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

In U.S. and foreign controlled studies, the frequency of serious adverse reactions reported was very low. Of 702 patients, 11.8% reported adverse reactions and in only 1.5% was glipizide discontinued.

Hypoglycemia: See PRECAUTIONS and OVERDOSAGE sections.

Gastrointestinal: Gastrointestinal disturbances are the most common reactions. Gastrointestinal complaints were reported with the following approximate incidence: nausea and diarrhea, one in seventy; constipation and gastralgia, one in one hundred. They appear to be dose-related and may disappear on division or reduction of dosage. Cholestatic jaundice may occur rarely with sulfonylureas: Glipizide should be discontinued if this occurs.

Dermatologic: Allergic skin reactions including erythema, morbilliform or maculopapular eruptions, urticaria, pruritus, and eczema have been reported in about one in seventy patients. These may be transient and may disappear despite continued use of glipizide; if skin reactions persist, the drug should be discontinued. Porphyria cutanea tarda and photosensitivity reactions have been reported with sulfonylureas.

Hematologic: Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia, and pancytopenia have been reported with sulfonylureas.

Metabolic: Hepatic porphyria and disulfiram-like reactions have been reported with sulfonylureas. In the mouse, glipizide pretreatment did not cause an accumulation of acetaldehyde after ethanol administration. Clinical experience to date has shown that glipizide has an extremely low incidence of disulfiram-like alcohol reactions.

Endocrine Reactions: Cases of hyponatremia and the syndrome of inappropriate antidiuretic hormone (SIADH) secretion have been reported with this and other sulfonylureas.

Miscellaneous: Dizziness, drowsiness, and headache have each been reported in about one in fifty patients treated with glipizide. They are usually transient and seldom require discontinuance of therapy.

Laboratory Tests: The pattern of laboratory test abnormalities observed with glipizide was similar to that for other sulfonylureas. Occasional mild to moderate elevations of SGOT, LDH, alkaline phosphatase, BUN and creatinine were noted. One case of jaundice was reported. The relationship of these abnormalities to glipizide is uncertain, and they have rarely been associated with clinical symptoms.

OVERDOSAGE

There is no well documented experience with glipizide overdosage. The acute oral toxicity was extremely low in all species tested (LD_{50} greater than 4 g/kg).
Overdosage of sulfonylureas including glipizide can produce hypoglycemia. Mild hypoglycemic symptoms without loss of consciousness or neurologic findings should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring should continue until the physician is assured that the patient is out of danger. Severe hypoglycemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to 48 hours since hypoglycemia may recur after apparent clinical recovery. Clearance of glipizide from plasma would be prolonged in persons with liver disease. Because of the extensive protein binding of glipizide, dialysis is unlikely to be of benefit.

DOSAGE AND ADMINISTRATION

There is no fixed dosage regimen for the management of diabetes mellitus with glipizide or any other hypoglycemic agent. In addition to the usual monitoring of urinary glucose, the patient's blood glucose must also be monitored periodically to determine the minimum effective dose for the patient: to detect primary failure, i.e., inadequate lowering of blood glucose at the maximum recommended dose of medication; and to detect secondary failure, i.e., loss of an adequate blood-glucose-lowering response after an initial period of effectiveness. Glycosylated hemoglobin levels may also be of value in monitoring the patient's response to therapy.
Short-term administration of glipizide may be sufficient during periods of transient loss of control in patients usually controlled well on diet.
In general, glipizide should be given approximately 30 minutes before a meal to achieve the greatest reduction in postprandial hyperglycemia.

Initial Dose: The recommended starting dose is 5 mg, given before breakfast. Geriatric patients or those with liver disease may be started on 2.5 mg.

Titration: Dosage adjustments should ordinarily be in increments of 2.5-5 mg, as determined by blood glucose response. At least several days should elapse between titration steps. If response to a single dose is not satisfactory, dividing that dose may prove effective. The maximum recommended once daily dose is 15 mg. Doses above 15 mg should ordinarily be divided and given before meals of adequate caloric content. The maximum recommended total daily dose is 40 mg.

Maintenance: Some patients may be effectively controlled on a once-a-day regimen, while others show better response with divided dosing. Total daily doses above 15 mg should ordinarily be divided. Total daily doses above 30 mg have been safely given on a b.i.d. basis to long-term patients.
In elderly patients, debilitated or malnourished patients, and patients with impaired renal or hepatic function, the initial and maintenance dosing should be conservative to avoid hypoglycemic reactions (see PRECAUTIONS section).

Patients Receiving Insulin: As with other sulfonylurea-class hypoglycemics, many stable non-insulin-dependent diabetic patients receiving insulin may be safely placed on glipizide. When transferring patients from insulin to glipizide, the following general guidelines should be considered:

For patients whose daily insulin requirement is 20 units or less, insulin may be discontinued and glipizide therapy may begin at usual dosages. Several days should elapse between glipizide titration steps.

For patients whose daily insulin requirement is greater than 20 units, the insulin dose should be reduced by 50% and glipizide therapy may begin at usual dosages. Subsequent reductions in insulin dosage should depend on individual patient response.

Several days should elapse between glipizide titration steps.

During the insulin withdrawal period, the patient should test urine samples for sugar and ketone bodies at least three times daily. Patients should be instructed to contact the prescriber immediately if these tests are abnormal. In some cases, especially when patient has been receiving greater than 40 units of insulin daily, it may be advisable to consider hospitalization during the transition period.

Patients Receiving Other Oral Hypoglycemic Agents: As with other sulfonylurea-class hypoglycemics, no transition period is necessary when transferring patients to glipizide. Patients should be observed carefully (1-2 weeks) for hypoglycemia when being transferred from longer half-life sulfonylureas (e.g., chlorpropamide) to glipizide due to potential overlapping of drug effect.

HOW SUPPLIED: **5 mg tablets** in HDPE, round, white, bottles of 100 (NDC 51285-598-02), 500 (NDC 51285-598-04), and 1000 (NDC 51285-598-05).
10 mg tablets in HDPE, round, white, bottles of 100 (NDC 51285-599-02), 500 (NDC 51285-599-04), and 1000 (NDC 51285-599-05).
The **5 mg tablet** is white, dye-free, round-shaped with H114 debossed on one side and bisect score on the other side; **10 mg tablet** is white, dye-free, round-shaped, with H115 debossed on one side and bisect score on the other side.

STORAGE: Store below 30°C (86°F).

DURAMED PHARMACEUTICALS, INC.
CINCINNATI, OH 45213 USA

100309
Iss. 5/97

Printed in USA

GLIPIZIDE
TABLETS, USP

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074550

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 5

2. ANDA # 74-550

3. NAME AND ADDRESS OF APPLICANT
Duramed Pharmaceuticals
5040 Lester Road
Cincinnati, Ohio 45231

4. BASIS OF SUBMISSION
Acceptable per CR # 1.
The listed drug product is Glucotrol® Tablets, 5 mg and 10 mg (Roerig). The listed drug product, covered by Patent # 3,669,966 expired on April 21, 1992 and exclusivity has expired on May 8, 1994.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME
None used

7. NONPROPRIETARY NAME
Glipizide Tablets, 5 mg & 10 mg

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
FIRM:
Original Submission: 10-10-94
Amendment: 11-8-94
NC: 5-15-96
NC: 6-14-96
NC: 9-20-96 (Letter from Hallmark for transfer of ownership to Duramed)
NC: 9-25-96 (Letter from Duramed for notify transfer of ownership of this ANDA)
Major Amendment: 1-8-97 (Response of NA letter dated 3-15-95)
Minor Amendment: 6-11-97 (Response to NA letter dated 5-23-97)
Facsimile Amendment: 7-7-97
* Minor Amendment: 8-5-97 (Response to 7-25-97 NA letter)

FDA:
Refusal to file Letter: 10-25-94
Accepted for filing: 11-10-94 (Acknowledgment letter date 11-23-94)
NA letter: 3-15-95
Acknowledgment letter: 2-14-97 (Transfer of ANDA from Hallmark to Duramed in response of 9-25-96)
NA letter (Minor amendment): 5-23-97
NA letter (Minor Amendment): 7-7-97
NA letter (Minor amendment): 7-25-97

10. PHARMACOLOGICAL CATEGORY
Hypoglycemic Agent

11. Rx or OTC Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Tablets

14. POTENCY
5 mg & 10 mg

15. CHEMICAL NAME AND STRUCTURE
Listed in proposed labeling insert per USP 23.

16. RECORDS AND REPORTS N/A

17. COMMENTS
Firm submitted adequate information to support this ANDA for its approval.

18. CONCLUSIONS AND RECOMMENDATIONS
Approved pending acceptable status of EER.

19. REVIEWER:
Mujahid L. Shaikh

DATE COMPLETED:
8-19-97

cc: AND 75-050
DUP File
Division File
Field Copy
Reading File

Endorsements:
HFD-625/M.Shaikh/8-19-97
HFD-625/M.Smela/S.Sherken for/8-20-97
HFD-617/S.O'Keefe, PM/8-22-97
x:\new\firmsam\duramed\ltrs&rev\74550rev.5
F/T by: bc/8-25-97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074550

BIOEQUIVALENCE REVIEW(S)

APR 7 1995

Glipizide Tablets
5 mg and 10 mg
ANDA #74-550
Reviewer: Moheb H. Makary
WP. 74550SDW.N94

Hallmark Pharmaceuticals, Inc.
Somerset, New Jersey
Submission Date:
November 8, 1994

Review Of Bioequivalence Studies, Dissolution Data And Request For a Waiver

I. Objective:

The firm has submitted two in vivo bioequivalence studies (under fasting and nonfasting conditions) for its 10 mg Glipizide Tablets, and dissolution data to compare the bioavailability of Hallmark and Pfizer (Glucotrol) 10 mg Glipizide Tablets following a single 10 mg dose.
The firm has also requested waiver of in vivo bioequivalence study requirements for its 5 mg Tablets. To support the request, the firm has submitted comparative dissolution profile for its Glipizide 5 mg Tablets versus Glucotrol® 5 mg Tablets. The formulations for Glipizide 5 mg and 10 mg Tablets (Hallmark) were also submitted.

II. Introduction:

Glipizide is an oral blood-glucose-lowering drug of the sulfonylurea class. The mechanism of action of glipizide in humans appears to be lowering the blood glucose concentration by stimulating the release of insulin from beta cells of the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. To achieve maximum reduction in postprandial blood glucose concentration, glipizide should be administered 30 minutes before a meal. Fasting insulin levels are not elevated even on long-term glipizide administration, but the postprandial insulin response continues to be enhanced after at least 6 months of treatment.

Glipizide is rapidly and completely absorbed after oral administration with a bioavailability of 95%. It is 98.4% bound to plasma proteins, reaches C_{max} in 1-3 hours, has an elimination half-life of 2-5 hours and volumes of distribution of 11 liters. The metabolic and excretory patterns are similar with oral or intravenous administration , indicating the first-pass metabolism is not significant. The metabolism of glipizide is extensive and occurs mainly in the liver. The primary metabolites are inactive hydroxylation products and polar conjugates and are excreted mainly in the urine. Total absorption and disposition of and oral dose was unaffected by food in normal volunteers, but absorption was delayed by about 40 minutes. Plasma glipizide levels of 20-90 ng/mL have been reported to be therapeutically effective.

Glipizide is indicated as an adjunct to diet for the control of hyperglycemia. Glipizide is commercially available as tablets of

2.5, 5 mg and 10 mg, Glucotrol[R], manufactured by Roerig Division, Pfizer Inc.. There is no fixed dosage regimen for management of diabetes mellitus with Glipizide. In addition to the usual monitoring of urinary glucose, the patient's blood glucose must also be monitored periodically to determine the minimum effective dose for the patient.

III. Protocol #930154 For Single-Dose, Two-Way Crossover Bioavailability Study of Glipizide 10 mg Tablet Under Fasting Conditions:

Study site:

Sponsor: Hallmark Pharmaceuticals, Inc.
Somerset, New Jersey

Investigators:

Medical Director:

Director. Pharmacokinetics:

Study design: Single-dose, randomized, 2-way crossover study under fasting conditions

Subjects: Twenty-four (24) and four alternates healthy adult male volunteers were selected to participate in this study. All twenty-eight (28) subjects successfully completed the study. As indicated in the protocol, statistical analysis was performed using data from subject Nos. 1-24.

Inclusion criteria: The subjects were between 18 and 45 years old. They were within 15% of their ideal weights (Table of "Desirable Weights of Adults", Metropolitan Life Insurance Company, 1983). Each subject received a complete physical examination and laboratory tests of hematopoietic, hepatic and renal functions. Only medically healthy subjects with clinically normal laboratory profiles and negative urine drug and alcohol prior to each phase were enrolled in the study.

Exclusions: Subjects with history or presence of:
-cardiovascular, pulmonary, hepatic, renal, hematological or significant gastrointestinal

disease;
-hypersensitivity or idiosyncratic reaction to glipizide or other sulfonylurea-type drugs;
-hypoglycemia, diabetes, or complications.
were excluded from the study.

Restrictions: The consumption of alcohol beverages, xanthine and caffeine containing foods were prohibited for 24 hours, before dosing and throughout the period of sample collection. Subjects were instructed to take no medication (including over-the-counter products) for 7 days preceding the study.

Dose and treatments: All subjects completed an overnight fast before any of the following drug treatments:

Test product: A. 1x10 mg Glipizide Tablet (Hallmark), lot #940302, Exp. N/A, lot size Tablets, content uniformity 101.6% (CV=1%), potency 100.1% (CV=3.5).

Reference product: B. 1X10 mg Glucotrol^{R} Tablet (Pfizer), lot # 38P077A, Exp. 12/98. potency 98.7%.

Food and fluid intake: Subjects fasted overnight before dosing and for 4 hours thereafter. Water was restricted 1 hour before and after dosing, but allowed at all other times. Standard meals were provided at 4 and approximately 9 hours after drug administration and at appropriate times thereafter.
At the time of dosing, each subject received 240 mL of sucrose solution containing the equivalent of three teaspoons of sugar to minimize hypoglycemic effects. Also, a sugar solution (containing the equivalent of 3 teaspoons of sugar dissolved in 60 mL of water) was administered at the following times after dosing: 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.50, 3.75 and 4 hours. Blood glucose was measured by glucometer prior to dosing and at 1, 2, 4, and 6 hours post-dose.

Blood samples: 10 mL blood samples were collected at: 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, and 36 hours. Blood samples were centrifuged and the resultant plasma was

separated. Plasma samples were frozen and stored at -22°C, pending assay .

Washout period: One week

Assay methodology:

Specificity:

Recovery:

Sensitivity:

Linearty:

Precision:

Stability:

Statistical Analysis:

ANOVA was performed at an alpha = 0.05 using the SAS-GLM. The 90% confidence intervals (2 one-sided t-test method) were calculated for LNAUC(0-t), LNAUCinf and LNCmax.

IV. In Vivo Results:

A total of 28 healthy male volunteers enrolled in and completed the study. Statistical analysis was performed using data from subject Nos. 1-24. Subject #27 was examined by a physician due to medical events. In period 2, the subject began to experience mild tiredness 19 minutes after dosing. This event was followed by dizziness, nausea, headache, and sweating at approximately 3.5 hours post-dose and was given extra sugar solution. Upon examination of the subject, the Medical Designate noted that the subject had no sweating, tremors, or tremulousness and requested that the subject be observed. The blood glucose level was 4.4 mmol/L, that the

subject was to have his lunch, and that the subject felt tired but was otherwise back to normal. The medical events were resolved by 4.3 hours after period 2 dosing and were judged by the Medical Director to be probably related to the study drug.

All adverse events are summarized in Table I and they were equally distributed between test and reference product. With the exception to subject #27, no medication was required for any event.

The plasma samples from subject Nos 1-24 were assayed for glipizide. The plasma concentrations and pharmacokinetic parameters are summarized in Table II.

Table II

Mean Plasma Concentrations And Pharmacokinetic Parameters
Following An Oral Dose of 10 mg (1x10 mg Tablet)
Glipizide Under Fasting Conditions
(N=24)

Time (hr)	Hallmark Test product Lot #940302 ng/mL (C.V.)	Pfizer Reference product Lot #38P077A ng/mL (C.V.)
0	0.00	0.00
0.5	247.14 (68.3)	178.27 (93.1)
1	399.08 (61.6)	284.68 (70.5)
1.5	439.19 (53.8)	376.03 (57.6)
2	475.00 (49.8)	450.10 (50.8)
2.5	476.06 (40.3)	490.01 (42.1)
3	498.47 (33.7)	509.40 (42.6)
3.5	511.44 (30.9)	488.36 (37.6)
4	506.13 (33.0)	498.35 (33.4)
5	411.11 (30.5)	471.53 (32.1)
6	351.21 (38.6)	341.39 (35.2)
8	235.66 (53.1)	241.69 (48.4)
10	169.63 (65.2)	178.21 (55.6)
12	112.31 (71.7)	130.31 (70.0)
16	59.36 (77.2)	68.36 (84.2)
24	19.93 (148.4)	22.11 (152.0)
36	1.57 (489.9)	2.00 (489.9)

	Test	Reference	90% CI
AUC (0-t)(ng.hr/mL)	4413.4(33.6)	4445.4(38.8)	
AUCinf (ng.hr/mL)	4641.2(33.6)	4660.7(38.6)	
Cmax (ng/mL)	704.1(17.7)	674.6(22.9)	
Tmax (hr)	2.93	3.25	
Kel (1/hr)	0.169	0.169	
Half-life (hr)	4.425	4.447	
LNAUC (0-t)			96.6-103.6%
LNAUCinf			94.8-100.7%
LNCmax			97.9-113.5%

1. Hallmark's test product had an AUC(0-t) of 4413.4 ng.hr/mL and AUCinf of 4641.2 ng.hr/mL, which were 0.7% and 0.4%, respectively, lower than their reference product values. The differences were not statistically significant. The 90% confidence intervals were within the acceptable range of 80-125% for log-transformed AUC(0-t) and AUCinf.

2. The Cmax of Hallmark's test product was 704.1 ng/mL which was 4.3% higher than its reference product value. The difference was not statistically significant . The 90% confidence interval of the test mean was within the acceptable range of 80-125% of the reference mean.

3. Glipizide plasma levels peaked at 3.5 and 3 hours for the test and reference products, respectively, following their administration under fasting conditions.

4. A statistically significant period effect was observed for Cmax and AUCinf.

V. Protocol #930155 For Post-Prandial Single-Dose Bioequivalence Study of Glipizide 10 mg Tablet:

Objective: The objective of this study was to compare the bioavailability of Hallmark's 10 mg Glipizide Tablet and Pfizer's Glucotrol® 10 mg Tablet under fasting and nonfasting conditions.

Study site:

Investigators: Please see Protocol #930154 above.

Study design: Open-label, randomized, three-way crossover study.

Subjects:	Eighteen healthy male subjects were enrolled in the study.
Selection criteria, Exclusion criteria and Prohibitions:	Please see Protocol #930154 above.
Dose and treatment:	A. 1x10 mg Glipizide Tablet (Hallmark), lot #940302, administered following an overnight fast. B. 1x10 mg Glipizide Tablet (Hallmark), lot #940302, administered 30 minutes after a standard breakfast preceded by an overnight fast. C. 1x10 mg Glucotrol^{R} (Pfizer), lot #38P077A, administered 30 minutes after a standard breakfast preceded by an overnight fast.
Food an Fluid intake:	Subjects on regimen A fasted overnight before dosing and for 4 hours thereafter. Subjects on regimen B and C fasted overnight and 30 minutes prior to dosing when a standard breakfast was administered. The standard breakfast consisted of 1 buttered English muffin, 1 fried egg, 1 slice of American cheese, 1 slice of Canadian bacon, 120 g of hashed browned potatoes, 180 mL of orange juice, and 240 mL of whole milk. Each dose was administered with 240 mL of 20% sugar solution to minimize hypoglycemic effects. Furthermore, 60 mL of 20% sugar solution was administered every 15 minutes for 4 hours. A standard meal was provided at 4 hours after drug administration.
Washout period:	One week between doses.
Blood collection:	Blood samples were collected at 0 (pre-dose) and at the following times after dosing: 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24 and 36 hours. Blood samples were centrifuged. Plasma samples were frozen and stored at -22°C pending assay .
Assay Methodology:	Please see Report #930154 above.

Statistical Analysis:

AUC(0-t), AUCinf, Cmax, Kel, T1/2 were determined and the concentrations at each sampling time point were reported.

VI. In Vivo Results:

Eighteen (18) subjects enrolled in the study and all eighteen subjects successfully completed the study. Subject #10 was enrolled in the study despite having deviated from 7 day restriction period for medication. Subject #10 took Seldane® tablets up until approximately 6 days prior to period 1 dosing. The Medical Designate judged the subject eligible to be enrolled in the study. All post-dose medical events are summarized in Table V. There were no serious adverse events or any events which required terminating any subjects from the study. No medication was required for any event.

The plasma concentrations and pharmacokinetic parameters of Glipizide are summarized in Table III.

Table III

Mean Plasma Glipizide Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 1x10 mg Glipizide Tablet Under Fasting and Nonfasting Conditions
(N=18)

Time hr	Treatment A Hallmark fasting Lot #940302 ng/mL (CV%)	Treatment B Hallmark Nonfasting Lot #940302 ng/mL (CV%)	Treatment C Pfizer Nonfasting Lot #38P077A ng/mL (CV%)
0	0	0	0
0.5	149.7(145.3)	24.6(178.4)	35.2(211.9)
1	210.3(100.9)	161.4(137.9)	163.9(118.1)
1.5	245.2(81.0)	241.8(86.5)	276.6(87.0)
2	283.0(73.0)	363.5(63.5)	418.4(68.6)
2.5	269.3(76.2)	377.6(48.0)	428.2(53.7)
3.0	250.1(65.1)	375.3(43.8)	434.2(46.6)
3.5	245.3(64.5)	387.5(32.9)	414.6(43.7)
4	273.2(60.1)	418.2(34.9)	405.3(34.5)
5	407.2(37.6)	394.4(29.4)	368.1(35.0)
6	451.1(35.1)	417.6(29.0)	361.4(30.2)
8	364.3(39.4)	334.3(40.0)	317.7(47.3)
10	282.8(43.5)	256.9(49.6)	219.8(57.2)
12	177.1(46.5)	156.2(50.2)	155.1(67.6)
16	77.7(47.8)	83.6(70.5)	72.1(75.5)
24	17.4(89.3)	17.2(76.3)	13.5(106.4)
36	0	0	0

				B/C
AUC(0-t) (ng.hr/mL)	4407.1(24.4)	4489.4(21.7)	4251.8(22.6)	1.05
AUCinf (ng.hr/mL)	4594.7(23.3)	4673.7(21.3)	4418.7(22.2)	1.05
Cmax(ng/mL)	597.1(21.2)	589.8(21.8)	614.6(30.3)	0.96
Tmax (hr)	4.8	4.1	4.3	
Kel(1/hr)	0.193	0.202	0.196	
T1/2(hr)	3.76	3.51	3.66	

1. For Hallmark's Glipizide, the mean AUC(0-t) and AUCinf values are 5.6% and 5.8% higher, respectively, than the reference product values under nonfasting conditions. The ratios of the test mean to the reference mean are within the acceptable range of 0.8-1.2 for AUC(0-t) and AUCinf.

2. For the test product, the mean Cmax value is 4.0% lower than the reference product value under nonfasting conditions. The ratio of the test mean to the reference mean is 0.96, which is within the acceptable range of 0.8-1.2 for Cmax.

3. Under nonfasting conditions, Tmax decreased by about 15% compared to fasting conditions. It seems that fasting delays absorption while a high fat meal do not change Cmax or AUC.

4. The Glipizide plasma concentrations peaked at 4 and 3 hours for the test and reference products, respectively, under nonfasting conditions, and at 6 hours for the test product under fasting conditions.

VII. Formulations:

The inactive ingredients for the reference product (Glucotrol®) are: colloidal silicon dioxide, lactose, microcrystalline cellulose, starch and stearic acid.

Hallmark's comparative formulations for Glipizide Tablets 5 mg and 10 mg are shown below:

Ingredient (amount per tablet)	5 mg	10 mg
Glipizide USP	5.0	10.0
Lactose Anhydrous NF		
Microcrystalline Cellulose, NF		
Corn Starch, NF		
Silicon Dioxide, NF		
Stearic Acid, NF		
	200.0	400.0

VIII. In Vitro Dissolution Testing:

Method:	USP XXII apparatus II (paddle) at 50 rpm
Medium:	900 mL of Simulated intestinal fluid TS (without pancreatin).
Number of Tablets:	12
Specifications:	NLT in 45 minutes
Test Products:	Hallmark's Glipizide 5 mg Tablets, lot #940303 10 mg Tablets, lot #940302
Reference Products:	Pfizer's Glucotrol® 5 mg Tablets, lot #38P081A 10 mg Tablets, lot #38P077A

Dissolution testing results are shown in Table IV.

IX. Comments:

1. The confidence intervals for LNAUC(0-t), LNAUCinf and LNCmax are within the acceptable range of 80-125% under fasting conditions. The ratios of the test mean to the reference mean are within the acceptable range of 0.8-1.2 for the above parameters under nonfasting conditions.

2. The in vitro dissolution testing for the test products, 5 mg and 10 mg strengths, is acceptable.

3. The formulation for Glipizide 5 mg strength is proportionally similar to the 10 mg strength of the test product.

X. Deficiency: None

XI. Recommendations:

1. The single-dose bioequivalence studies under fasting and nonfasting conditions conducted by Hallmark Pharmaceuticals, Inc., on its Glipizide 10 mg Tablets, lot #940302, comparing it to Glucotrol® 10 mg Tablets manufactured by Pfizer Inc., have been found acceptable by the Division of Bioequivalence. The studies demonstrated that Hallmark's Glipizide 10 mg tablet is bioequivalent to the reference product Glucotrol® 10 mg Tablet manufactured by Pfizer Inc.

2. The dissolution testing conducted by Hallmark Pharmaceuticals, Inc., on its Glipizide 10 mg Tablets, lot #940302, and 5 mg Tablets, lot #940303, comparing them with the respective strengths of Pfizer's Glucotrol® 10 mg and 5 mg Tablets is acceptable. The formulation for the 5 mg strength is proportionally similar to the 10 mg strength of the test product which underwent bioequivalence testing. Waiver of in vivo bioequivalence study requirements for

the 5 mg tablet of the test products is granted. The Division of Bioequivalence deems Glipizide 5 mg tablet manufactured by Hallmark Pharmaceuticals, Inc., to be bioequivalent to Glucotrol® 5 mg Tablet manufactured by Pfizer Inc.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of SIF (without enzyme) pH 7.5 at 37°C using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following specification:

> Not less than of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

4. From the bioequivalence point of view, the firm has met the requirements of in vivo bioequivalence and in vitro dissolution testing and the application is approvable.

The firm should be informed of the above recommendations.

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED MPARK
FT INITIALLED MPARK Date: 4/4/95

Concur: _____ Date: 4/7/95
Rabindra N. Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

MMakary/4-1-95 wp 74550SDW.N94
cc: ANDA #74-550, original, HFD-600 (Hare), HFD-630, HFC-130 (JAllen), HFD-344 (CViswanathan), HFD-658 (Park, Makary), Drug File, Division File.

Table IV. In Vitro Dissolution Testing

Drug (Generic Name): Glipizide Tablets
Dose Strength: 5 mg and 10 mg
ANDA No.:74-550
Firm: Hallmark Pharmaceuticals, Inc.
Submission Date: November 8, 1994
File Name: 74550SDW.N94

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: 900 mL of SIF (without enzzyme)
Specifications: NLT in 45 minutes
Reference Drug: Glucotorl
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 940303 Strength(mg) 5			Reference Product Lot # 38P081A Strength(mg) 5		
	Mean %	Range	%CV	Mean %	Range	%CV
15	96.9		1.3	101.9		3.6
30	96.6		1.0	101.3		3.3
45	96.8		1.1	100.4		3.1
60	97.0		0.9	101.5		3.2

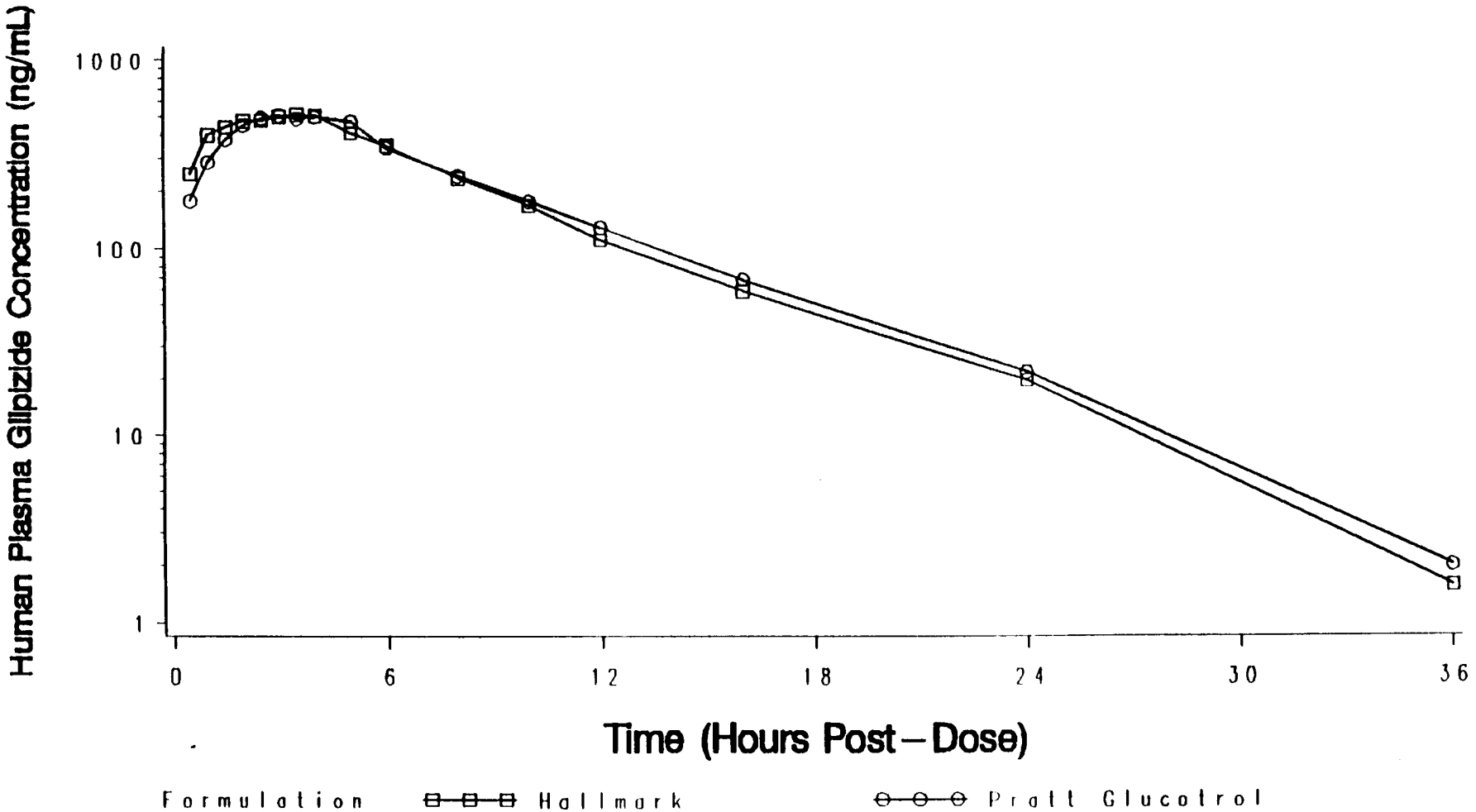
Sampling Times (Minutes)	Test Product Lot #940302 Strength(mg) 10			Reference Product Lot # 38P077A Strength(mg) 10		
	Mean %	Range	%CV	Mean %	Range	%CV
15	96.3		2.6	90.5		5.0
30	97.8		1.7	97.0		2.6
45	98.0		1.4	97.6		1.6
60	98.1		1.4	98.2		1.4

Figure 1

Project No. 930154

Mean Human Plasma Glipizide Concentrations

(Semi – Log Plot)



6-017

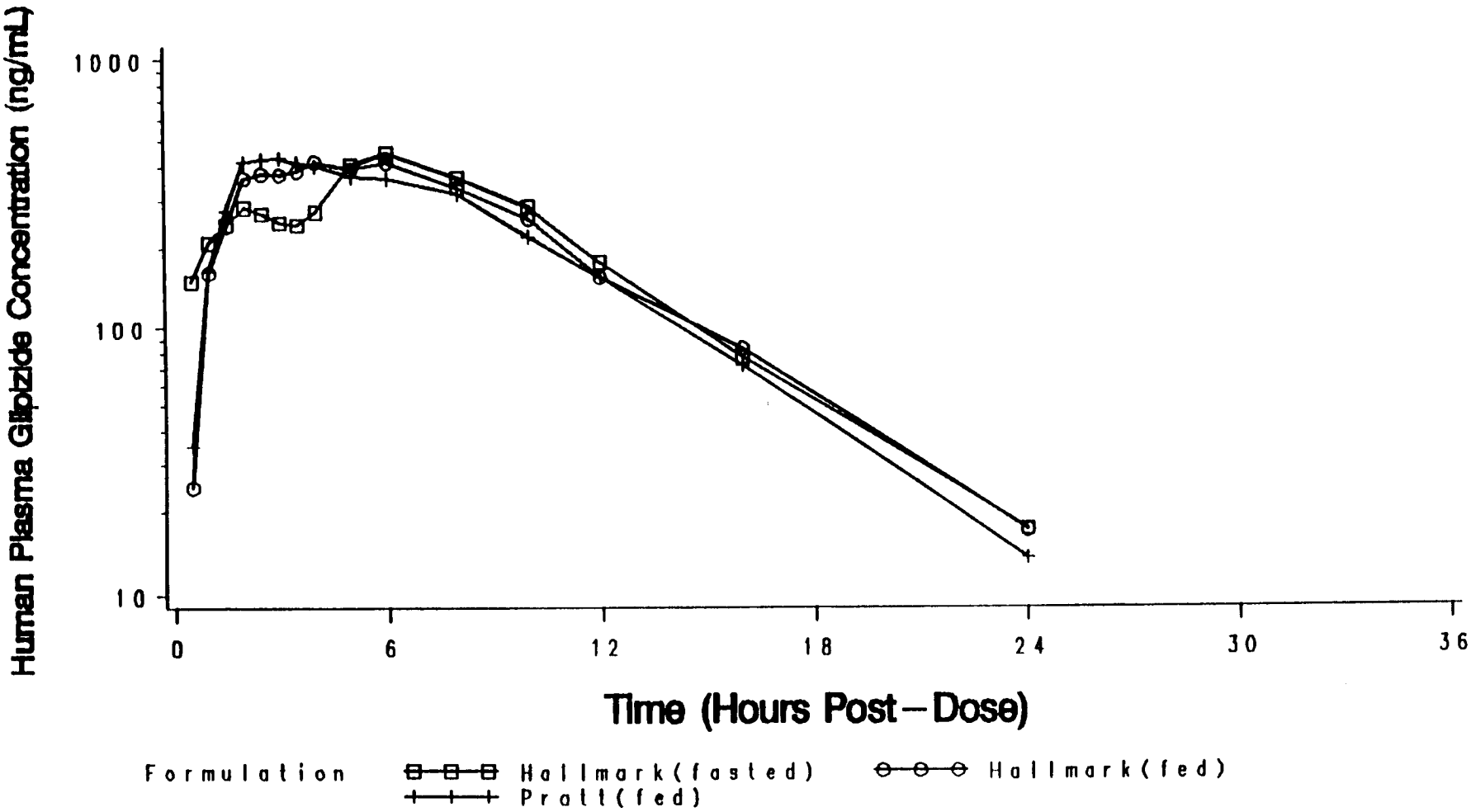
IB/Consent | Protocol | Subject Data/Profiles

Figure 1

Project No. 930155

Mean Human Plasma Glipizide Concentrations

(Semi – Log Plot)



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